REMARKS

Claims 11-23 were pending prior to this amendment. Claims 11, 19, 21 and 23 are hereby amended and new claims 24-33 have been added. Therefore, claims 11-33 are currently pending.

The Invention

The present invention relates to a vaccine formulation that includes a mixture of a virus-like particle (VLP) formed from a surface antigen of a virus, and a non-living vaccine antigen. Additional vaccine antigens may be added to the mixture. The formulation is suitable for mucosal administration.

The VLP acts as an adjuvant, enhancing the immune response to the non-living vaccine antigen. The immune response to the surface antigen may also be enhanced by the vaccine antigen. Thus, the vaccine formulation provides a adjuvant effect enhancing the response to the VLP or to the vaccine antigen components or both.

In a particular embodiment, the vaccine formulation is a mixture of a Hepatitis B surface antigen (HBsAg) virus-like particle. In another embodiment, the vaccine antigen is a viral nucleocapsid antigen, such as the Hepatitis B nucleocapsid antigen, the Human Papilloma virus nucleocapsid antigen or the Hepatitis C nucleocapsid antigen.

The vaccine of the present invention may be administered as a preventative vaccine, prior to infection or disease involving the virus from which the VLP is derived, or the disease agent from which the vaccine antigen is derived.

Alternatively, the vaccine may be administered as a therapeutic vaccine after infection or during the course of disease involving the virus from which the VLP is derived, or the disease agent from which the vaccine antigen is derived.

Objections listed in the Office Action of December 4, 2001

In the Office Action issued on December 4, 2001, the Examiner objected to Figure 5 of the drawings because the text within the drawing is in the spanish language.

Applicants will provide formal drawings with the English annotation to Figure 5 upon allowance of patentable subject matter from the present application. The Examiner is respectfully requested to hold this objection in abeyance until claims are allowed at which time the formal drawings with the English annotation will be submitted.

The Examiner also objected to claim 21, stating that claim 21 drawn to a vaccine suitable for mucosal administration did not further narrow claim 11 drawn to a nasal vaccine.

Applicants have amended claim 11 to recite a vaccine suitable for mucosal administration and have also amended claim 21 to recite the embodiment wherein the mucosal administration is

nasal administration. Therefore, Applicants assert that this objection is moot and should be withdrawn, which action is respectfully requested.

Rejections under §112, second paragraph

In the Office Action of December 4, 2001, claims 11-23 were rejected under §112, second paragraph for the recitation of "...antigen synergizing in adjuvant effect..." According to the Examiner, it cannot be determined what is intended by this phrase.

The Examiner asks, does the administration of the surface antigens have a synergistic effect on the immune response in general? Or, is the immune response augmented specifically to both antigens? Or, is the immune response to the surface antigen specifically enhanced when the vaccine antigen is administered in conjunction with the surface antigen? Also, the Examiner continues, in view of the choice of nomenclature of the "vaccine" antigen in the claims, does Applicant intend for the vaccine formulation to be prophylactic only against the virus supplying the vaccine antigen and not the surface antigen?

Applicants have amended claim 11 and added new claim 28. Claim 11 as amended recites "...a mixture of a) a virus-like particle (VLP) comprising a surface antigen from a virus, and b) a non-living vaccine antigen, said surface antigen having an adjuvant effect on said vaccine antigen,..."

New claim 28 recites "....wherein the immune response to the surface antigen and to said vaccine antigen are each enhanced."

Further, as described above in the section entitled "The Invention" the VLP acts as an adjuvant, enhancing the immune response to the non-living vaccine antigen. The immune response to the surface antigen may also be enhanced by the vaccine antigen. Thus, the vaccine formulation provides a adjuvant effect enhancing the response to the VLP or to the vaccine antigen components or both.

Applicants maintain that the nature and adjuvant effects of the claimed vaccines are clear and definite. The claimed vaccines are mixtures of a VLP and a vaccine antigen wherein the VLP enhances the immune response to the vaccine antigen and the vaccine antigen may enhance the immune response to the VLP. Therefore, the rejection of claims 11-23 under 37 C.F.R. §112, second paragraph is not applicable and should be withdrawn.

At page 3 of the Office Action of December 4, 2001 the Examiner rejected claims 16-18 under 37 C.F.R. §112, second paragraph as allegedly vague and indefinite in stating that the VLP comprises nucleocapsid antigens from hepatitis B (HBV), hepatitis C (HCV), or papilloma virus (HPV) nucleocapsid antigens. The Examine inquires whether the viral nucleocapsid protein is intended to be incorporated into a VLP? Or, are the VLPs hybrid molecules in which two distinct nucleocapsid proteins are fused together?

Applicants have amended claim 11 (from which claims 16-18 depend), to recite "...a mixture of a) a virus-like particle (VLP) comprising a surface antigen from a virus, and b) a non-living vaccine antigen, said surface antigen having an adjuvant effect on said vaccine antigen,..."

Therefore, Applicants maintain that claims 16-18 are clear and definite and the rejection under 37 C.F.R. §112, second paragraph is not applicable and should be withdrawn.

Also at page 3, the Examiner rejected claims 16-18 under 37 C.F.R. §112, second paragraph as allegedly vague because it cannot be discerned how an antigen is immuno-enhanced by another antigen. The Examiner asks whether it is intended for both antigens to have a synergistic effect on the immune system when administered together, or is the immune response more specific to the vaccine antigen if it is co-administered with HBsAg?

Applicants take this opportunity to remind the Examiner that there is no statutory requirement that the mechanism of the invention be known. Thus, Applicants are under no obligation to investigate, much less disclose "how an antigen is immuno-enhanced by another antigen." Further, Applicants maintain that as recited in amended claims 11 and 28 as explained above, the claimed adjuvant effects are clear and definite. Therefore, Applicants again assert that the rejection under 37 C.F.R. §112, second paragraph is not applicable and should be withdrawn.

At pages 3-4 of the Office Action, the Examiner rejected claims 15-18 under 37 C.F.R. §112, first paragraph for allegedly failing to provide a written description that reasonably conveys to one of skill in the art that the inventor(s) had possession of the invention at the time the application was filed. Specifically, the Examiner alleges that it cannot be discerned whether the VLPs containing nucleocapsid antigens of hepatitis B, hepatitis C, or papilloma virus are

mixed or fused. Further, the Examiner states, there is no support in the specification for VLPs of HCV, HBV, or HPV incorporating HBsAg. Moreover, according to the Examiner, the does not teach how the skilled artisan could identify a mixture, fusion or complex of HBsAg and the viral nucleocapsid that would satisfy the vaccine function. Lastly, the Examiner states that the specification does not teach possession of these complexes, fusions or mixtures, nor does the specification teach how to make the hybrid formulations.

As explained in detail above, the claimed VLPs and vaccine antigens of the claims, as amended, are mixed together. Further, in the Office Action of December 4, 2001 the Examiner has cited pages 5, line 28; page 6, line 3; and page7, line 19 as teaching "mixing" two antigens together. Thus, Applicants assert that the claimed mixtures of VLP and vaccine antigen are indeed described in the specification in such a way as to convey to one of skill in the art that the inventor had possession of the claimed invention at the time of filing of the application. Therefore, Applicants assert that the rejection of claims 15-18 under 37 C.F.R. §112, first paragraph is inappropriate and should be withdrawn.

At pages 4-6, the Examiner rejected claims 15-19 and 22 under 37 C.F.R. §112, first paragraph as allegedly failing to enable one of ordinary skill in the art to which it pertains, or is most nearly connected, to make and/or use the invention. According to the Examiner, it cannot be determined whether the claims are directed to treating and preventing both hepatitis B and the infectious disease caused by the agent from which the vaccine antigen is derived (such as HPV or HCV) or just hepatitis B.

In addition, the Examiner again questions whether the HBsAg is encapsulated within the various VLPs, or whether the VLPs and HBsAg are formed into a chimeric molecule or are simply provided in a mixture. However, the Examiner goes on to acknowledge the teachings in the specification of the mixing of antigens, and to the co-administration of the various antigens (in the Examples at page 7-11).

According to the Examiner, the specification fails to teach how to identify a mixture, fusion or complex of HBsAg and any viral nucleocapsid that would satisfy the intended vaccine function. The Examiner comments that the working examples in the specification are limited to administering combinations of antigens in mice and monitoring antibody response. Further, the Examiner offers the opinion that those of skill would have no way to predict how long the elevated antibody responses lasted after administration of the vaccines.

The Examiner then states that the specification does not present any data that would indicate to those of skill in the art that the mice developed an immune response sufficient to block HBV, HCV, HPV or any other virus as the vaccinated mice were not challenged with any virus. Further, according to the Examiner, the specification presents no animal model that would indicate that infection of hepatitis, papilloma or any other virus may be treated by the claimed vaccine compositions. The Examiner offers the Lanford et al. reference (ILAR Journal 42(2): 117-26, 2001) for the teaching that the Chimpanzee is the only acceptable animal model for HCV infection and states that the data showing an increased antibody response would not convince one of skill that the response was ameliorative or protective against HCV. Likewise, the Coursaget et al. reference (Cancer Surveys 33: 355-381, 1998) is cited for the teaching that

the some success has been achieved in mouse models for human papilloma virus infection, but "animal models more relevant to humans" have demonstrated only poor results. Finally, the Farrell et al. reference (Drugs 60(4): 701-710, 2000) is cited for the teaching that problems such as deleterious side effects still exist in developing HBV therapeutics for long term efficacy.

The Examiner summarizes by stating that it would require undue experimentation to practice the claims due to the alleged ambiguity of the claims; the scope of the claims to preventing and treating any infection with the vaccine composition; the lack of guidance for making chimeric/encapsulated molecules; the lack of guidance as to the CTL responses or the persistence of the antibody responses; the lack of an appropriate animal model or data demonstrating prevention or treatment by vaccine administration; and the lack of predictability in the vaccine art.

Claim 22 has been amended to recite "...wherein the vaccine formulation is suitable for use as a therapeutic vaccine against Hepatitis B virus (HBV) infection" and new claims 26 and 27 likewise recite "...wherein the vaccine formulation is suitable for use as a therapeutic vaccine against Hepatitis C virus (HCV) infection" and "...against Human Papilloma Virus (HPV) infection" respectively. Similarly, claims 23, 24 and 25 specifically recite preventative vaccines against HBV, HCV and HPV, respectively. Therefore, Applicants maintain that claim 22 and new claims 26 and 27 are clear and definite as to which disease is being treated and the rejection based on the Examiner's comment that "it cannot be determined whether the claims are directed to treating and preventing both hepatitis B and the infectious disease caused by the agent from

which the vaccine antigen is derived (such as HPV or HCV) or just hepatitis B." does not apply and should be withdrawn.

Applicants again point out that the amended claims are not ambiguous with respect to the composition of the claimed vaccines. As discussed at length above, the claimed vaccines are clearly defined and distinctly claimed as mixtures of a VLP and a vaccine antigen. Also, as acknowledged by the Examiner, the working examples in the specification clearly teach mixing of the VLP and the vaccine antigen. Therefore, the rejection based encapsulated or chimeric forms rather than mixtures of a VLP and a vaccine antigen cannot stand and should be withdrawn.

As to the Examiner's assertion that the specification does not teach the skilled artisan how to identify the mixture, fusion or complex of HBsAg and any viral nucleocapsid that would satisfy the intended vaccine function: Applicants have in the above response, already addressed the issue of the instant claims reciting mixtures of a VLP, such as that formed from HBsAg, and a vaccine antigen, such as a viral nucleocapsid rather than fusions or complexes.

To address the issue of whether the intended vaccine function of the claimed mixture is adequately taught as claimed, Applicants respectfully remind the Examiner that adjuvants are effective on the immune response to antigens in general. Therefore one of ordinary skill in the art would have a reasonable expectation that the instantly claimed vaccine mixture would be effective with any vaccine antigen.

Further, the present invention as claimed is not limited as to the longevity of the immune response to vaccination with the mixtures of the invention. Any prophylactic response against

HBV, HCV or HPV meets the requirements of claims 23, 24 or 25 respectively. Similarly, any therapeutic response against HBV, HCV or HPV meets the requirements of claims 22, 26 or 27 respectively.

In the Examples 3-5 at pages 9-11, and in figures 3-5 the specification teaches that HBsAg when mixed with a vaccine antigen enhances the immune response to the vaccine antigen and the vaccine antigen enhances the immune response to the HBsAg. The hepatitis core antigen (HBcAg) and a VLP (del VPH 16) of the human papilloma virus (HPV) were tested as vaccine antigens in the mixtures of the present invention. Based on these examples, one of ordinary skill in the art would have a reasonable expectation that the HBsAg would similarly provide an enhancing effect on the immune response to any other vaccine antigen. Furthermore, these demonstrated positive immune responses in the mouse model of immune response against viral infection would also lead one of ordinary skill to have a reasonable expectation of successful application of the vaccine mixtures of the present invention in prophylaxis and treatment.

Contrary to the Examiner's assertion, the Chimpanzee is not the only acceptable animal model currently available for study of HCV infections. In fact, the cited Lanford et al. abstract states that "The chimpanzee (Pan troglodytes) is the only experimental animal susceptible to infection with hepatitis C virus (HCV)." [Emphasis added]. This is distinct and different from the Examiner's characterization that the chimpanzee is the only acceptable animal model for study of HCV. Other animal models are routinely used and data from such models is used to support the initation of clinical trials. (See below).

The Coursaget et al. abstract cited by the Examiner, rather than dismissing animal models, actually provides support for the opposite view. At lines 4-10 of the third paragraph, Coursaget et al. states "Following the encouraging results obtained with both prophylactic and therapeutic papilloma vaccines in various animal models,....Phase I-II clinical trials are underway to assess the safety and immunogenicity of various VLP based prophylactic vaccines for HPV 11, 16 and 18 and phase III trials to assess their efficacy are being planned." Thus, Coursaget et al. provide the evidence that success in various animal models is accepted by those of skill in the vaccine art to initiate trials with (presumably) a reasonable expectation of success.

The Farrell reference is cited by the Examiner for the teaching that problems still exist in the development of HBV therapeutics, and for the observation that CTL attack on hepatitis core-presenting hepatocytes results in deleterious side effects. The instant claims make no assertions as to overcoming each and every problem in antiviral therapy, the claims merely recite a vaccine composition with therapeutic efficacy. Neither the specification nor the claims assert that the vaccines of the present invention are one hundred percent effective, or that there can be no unwanted side effects.

In order to fulfill the statutory requirements for patentability, Applicants are obliged to provide a disclosure which would lead the skilled artisan to have reasonable expectation of success in making or using the claimed vaccines according to the teachings of the specification. This is clearly provided by teachings of the immune responses observed with the exemplified vaccine mixtures disclosed in the present specification. It is not necessary, however, to overcome each and every problem in the development of a therapeutic vaccine.

For all these reasons, Applicants assert that it would not require undue experimentation to practice the claimed invention and that the pending claims are fully supported in their broadest scope by the specification as filed which teaches that a specific immune response to both the vaccine antigen and to the VLP are generated in the mouse model and that the VLP exerts a synergistic effect on the immune response to the vaccine antigen. Because such data are generally accepted by those of skill in the art as a reasonable basis for initiation of clinical trials, applicants assert that the burden of proof of demonstrating a reasonable expectation of success has been met.

Therefore, Applicants respectfully assert that the rejection of claims 15-19 and 22 under 37 C.F.R. §112, first paragraph should be withdrawn.

At page 7 of the Office Action the Examiner rejected claims 11-13, 20, 21 and 23 under 35 U.S.C. §102(e) as allegedly anticipated by Chatfield et al., U.S. 6,048,536. According to the Examiner, the Chatfield patent teaches a pharmaceutical product comprising influenza virus antigens, haemagglutinin (HA) and neuraminidase, administered intranasally by aerosol. (Claims 1, 2, 5, 6, 9-11. 14-16 and 19). Further, the Examiner asserts that the vaccine is formulated a liquid or dry powder, including preservatives and stabilizers (col. 3, lines 9-16).

Nowhere in the Chatfield patent is there any teaching of a virus-like particle (VLP) comprising a surface antigen from a virus as required in claim 11 and all dependent claims as currently pending. The disclosed viral surface antigens, HA and neuraminidase do not form VLPs. Therefore, the Chatfield patent cannot anticipate the pending claims and Applicants

respectfully request that that the rejection of claims 11-13, 20, 21 and 23 under 35 U.S.C. §102(e) for anticipation by Chatfield, U.S. 6,048,536 be withdrawn.

At page 8 of the Office Action the Examiner rejected claim 14 under 35 U.S.C. §103(a) as allegedly unpatentable over Chatfield (supra) in view of Fields ed. Virology, Volume 1, third edition, Philadelphia, Lippincott Williams and Wilkins, publishers, 1996: page 1356. While Chatfield does not teach the use of a second antigen in addition to the HA or neuraminidase, in the Examiner's view one of ordinary skill would have been motivated to incorporate another influenza virus antigen such as M_2, as disclosed in Fields at page 1356.

As pointed out above, nowhere in Chatfield is there any teaching of a virus-like particle (VLP) comprising a surface antigen from a virus as required in the claims as currently pending. The disclosure of Fields does nothing to fill this void. Thus, the result of the combination of the Chatfield and Fields references would still be short of the claimed invention.

Therefore, Applicants assert that the rejection of claim 14 under 35 U.S.C. §103(a) as allegedly unpatentable over Chatfield (supra) in view of Fields ed. must be withdrawn, which action is earnestly solicited.

Support for the amendments to the specification and claims

Several changes have been made to the second complete paragraph (lines 20-29) at page 4 to correct grammatical errors. A section entitled "Summary of the invention" has been inserted at page 5. This section is supported by the claims and the specification as filed. The figure

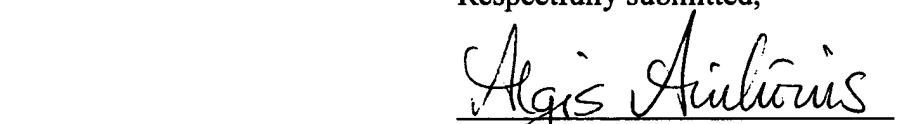
legends have been moved to the appropriate location after the summary of the invention and entitled "Brief description if the figures."

The amendments to claims 11, 19, 21, 22 and 23 are supported by the claims and the specification as filed. Claim 11 as amended is supported by the specification *inter alia* at page 6, lines 6-9; and Example 4 pages 10-11 and figure 4. Claim 19 as amended is supported by the specification *inter alia* by Examples 2-5 and figures 2-5. Claim 21 as amended is supported *inter alia* by claim 1 as filed. Claim 22 as amended is supported *inter alia* by the specification at page 7, first complete paragraph and by claim 10 as filed. New claims 24-33 are supported by the specification and the claims as originally filed.

No new matter has been added by these amendments.

If the Examiner has any questions or comments relating to the present application, he or she is respectfully invited to contact Applicants' attorney at the telephone number set forth below. Applicants submit that the application is now in condition for examination on the merits.

Respectfully submitted,



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EDITED VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification

At page 1, line 11 please delete "**Previous technique**" and insert in its place

- - **Background** - -

At page 4, please delete the second complete paragraph (lines 20-29) and replace with the following:

- - HBcAg has been demonstrated to be a very good carrier. HBcAg [represents] is a highly immunogenic antigen in human and animal models. HBcAg directly activates [directly] B cells and generates strong T cell responses[,]. [f]Furthermore, the efficient processing and presentation of HBcAg by the antigen presenting cells makes it an ideal carrier molecule. Hence a large number of epitopes [has] have been chemically linked or genetically fused to the HBcAg molecule to successfully increase their immunogenicity. Bacterial expression vectors [has] have been designed [in bacteria] to enable the insertion of heterologous B cell epitopes in different positions inside the particles of HBcAg and the efficient purification of hybrid particles. - -

At page 5, after line 22 and before the section entitled "**Detailed description of the invention**" please insert the following:

- - Summary of the invention

The present invention provides a vaccine formulation suitable for mucosal administration, the vaccine includes a mixture of a virus-like particle (VLP) comprising a surface antigen from a virus, and a non-living vaccine antigen, the surface antigen having an adjuvant effect on said vaccine antigen. Each vaccine dose includes up to about 1 milligram each of the surface antigen and vaccine antigen. The vaccine formulation may include one or more of the following: a preservative, a stabilizer and a second vaccine antigen.

In a particular embodiment the surface antigen is Hepatitis B virus surface antigen (HBsAg). The vaccine antigen may an antigen of a viral nucleocapsid, such as the nucleocapsid antigen of Hepatitis B virus, the nucleocapsid antigen of Human Papilloma-virus, or the nucleocapsid antigen of Hepatitis C virus.

Brief description of the figures

Figure 1. Three doses schedule (days 0, 14 and 28). Extraction was performed on day 42. Groups 1 and 2 were inoculated with 50 μL through the nasal route. Group 3 was inoculated subcutaneously with 100 μL.

Figure 2. Two doses schedule (days 0 and 14). Extraction was performed on day 21. Groups 1, 2 and 3 were inoculated with 50 μL through the nasal route. Group 4 was inoculated subcutaneously with 100 μL.

Figure 3. Three doses schedule (days 0, 14 and 28). Extraction was performed on day 26. Groups 1, 2, 3, 4 and 5 were inoculated through the nasal route. Group 6 was inoculated intramuscularly with 100 μL.

Figure 4. Two doses schedule (days 0 and 14). Extraction was performed on day 26. All groups were inoculated nasally with 50 μL. The composition of experimental groups is shown in the table added to the figure.

Figure 5. Three doses schedule (days 0, 14 and 28). Extraction was performed on day 42. Groups 1,2 and 3 were inoculated with 50 μL through the nasal route. - -

Please delete the section entitled "**DESCRIPTION OF FIGURES**" at page 11, line 28 to page 12, line12.

In the claims:

Please amend claims 11, 19 and 23, and add new claims 24-33 as follows: (All the pending claims 11-33 are recited below for the Examiner's convenience).

11. (Amended) A vaccine formulation suitable for [nasal] mucosal administration, comprising : a mixture of

a) a virus-like particle (VLP) comprising a surface antigen from a virus, and

b) a non-living vaccine antigen [synergizing in adjuvant effect with said surface antigen] , said surface antigen having an adjuvant effect on said vaccine antigen,

wherein the surface antigen and vaccine antigen are each present up to about 1 mg.

12. The vaccine formulation according to claim 11, further comprising a preservative.

13. The vaccine formulation according to claim 11, further comprising a stabilizer.

14. The vaccine formulation according to claim 11, further comprising a second vaccine antigen.

15. The vaccine formulation according to claim 11, wherein the surface antigen is Hepatitis B virus surface antigen (HBsAg) and the vaccine antigen is an antigen of a viral nucleocapsid.

16. The vaccine formulation according to claim 15, wherein the viral nucleocapsid is a virus-like particle comprising the nucleocapsid antigen of Hepatitis B virus.

17. The vaccine formulation according to claim 15, wherein the viral nucleocapsid is a virus-like particle comprising the nucleocapsid antigen of Human Papilloma-virus.

18. The vaccine formulation according to claim 15, wherein the viral nucleocapsid is a virus-like particle comprising the nucleocapsid antigen of Hepatitis C virus.

19. (Amended) The vaccine formulation according to claim 11, wherein the surface antigen is Hepatitis B virus surface antigen (HBsAg) and the vaccine antigen [is of any nature] comprises a single antigen or a mixture of different antigens that are immuno-enhanced by HBsAg.

20. The vaccine formulation according to claim 11, wherein the vaccine formulation is suitable for administration as a solid, liquid or spray.

21. (Amended) The vaccine formulation according to claim 11, wherein the vaccine formulation is suitable for [mucosal] nasal administration.

22. (Amended) The vaccine formulation according to claim 11, wherein the vaccine formulation is suitable for use as a therapeutic vaccine against Hepatitis B virus (HBV) infection.

23. (Amended) The vaccine formulation according to claim 11, wherein the vaccine formulation is suitable for use as a preventive vaccine against Hepatitis B virus (HBV) infection.

24. (New) The vaccine formulation according to claim 11, wherein the vaccine formulation is suitable for use as a preventive vaccine against Hepatitis C virus (HCV) infection.

25. (New) The vaccine formulation according to claim 11, wherein the vaccine formulation is suitable for use as a preventive vaccine against Human Papilloma virus (HPV) infection.

26. (New) The vaccine formulation according to claim 11, wherein the vaccine formulation is suitable for use as a therapeutic vaccine against Hepatitis C virus (HCV) infection.

27. (New) The vaccine formulation according to claim 11, wherein the vaccine formulation is suitable for use as a therapeutic vaccine against Human Papilloma virus (HPV) infection.

28. (New) The vaccine formulation according to claim 11, wherein the immune response to the surface antigen is enhanced.

29. (New) The vaccine formulation according to claim 11, wherein the immune response to said vaccine antigen is enhanced.

30. (New) The vaccine formulation according to claim 11, wherein the immune response to the surface antigen and to said vaccine antigen are each enhanced.

31. (New) The vaccine formulation according to claim 19, wherein the vaccine antigen comprises the core antigen of Hepatitis B virus.

32. (New) The vaccine formulation according to claim 19, wherein the vaccine antigen comprises the nucleocapsid antigen of Hepatitis C virus.

33. (New) The vaccine formulation according to claim 19, wherein the vaccine antigen comprises the nucleocapsid antigen of Human Papilloma-virus.